

Symposium on
Phenotypic Variation in Populations: Relevance
to Risk Assessment

Brookhaven National Laboratory, Upton, NY
December 7-10, 1986

Scope and Rationale

We are proposing to hold a Symposium on "Phenotypic Variation in Populations: Relevance to Risk Assessment" and are seeking financial support for this enterprise. The Symposium will take place from December 7 through Dec. 10, 1986 at Brookhaven National Laboratory, Upton, NY. We are requesting funds for travel costs and registration fees for invited speakers, and for scholarships that will enable graduate students and post-doctoral fellows to attend the Conference. We also hope to receive support to help defray the cost of putting together and running the Symposium.

Variability is a universal characteristic of sexually reproducing wild animal and plant species that develops as a result of spontaneous mutation or may develop in response to, and be maintained by the tremendous diversity of environmental regimes. Phenotypic variation has several sources; genetic, based upon allele differences in individuals; environmental, originating in conditions that are exogenous to organisms during their lifespan; developmental differences caused by somatic mutations or by activation of specific alleles due to pressures of a particular environment; and cytoplasmic traits, usually found in the egg and therefore, in humans, synonymous with maternal inheritance, that are transmitted over two or more generations. In the latter case there is no involvement with the DNA of the chromosomes.

The human race has enormous heterogeneity. Unlike wild animal populations where the last two sources of variation are less significant, and may be swamped out by genetic and environmental variation, all four sources contribute to the diversity of humans. Variability, therefore, is a vital dimension in any consideration of human risk assessment.

Risk assessment and the regulation of human exposure to mutagens, carcinogens, and teratogens is fraught with difficulties. Government agencies, industry, academia, and the law, rightly have been concerned with the reduction of risk to humans, and to the environment. The number of Symposia on risk assessment at its various levels, from molecular biology to management practices, reflect these concerns and the complexity of the issues involved. But in evaluating risk from a scientific standpoint, and in weighing and balancing the cost/benefit equation from a societal approach, we have generalized and formulated our standards for exposure in terms of a human selected at random from the population. Similarly, animal experiments frequently have used pure-bred homogeneous stocks, and have shelved the problem of variability.

How far can we ignore human variability in risk assessment? Should we be concerned with individuals who cluster at the extremes of the normal distribution curve? Several recent publications have highlighted the enormous variability in the physiological responses of humans; for example, the levels of the inducible enzyme aryl hydrocarbon hydrolase (AHH), that is dependent upon the presence of a single gene, may vary 30-fold in the normal human population. There are undoubtedly many examples of human variability in so-called normal populations that are highly relevant to risk assessment, and such high variability may not be unusual. Our knowledge of the highly polymorphic nature of DNA is growing rapidly due to new molecular techniques. There is apparently enormous diversity at the DNA level in the human population; the implications of this variability can already be seen to affect both public health and forensic issues.

A major sector of our population in which there are marked excursions from the average (standard) human values is amongst the elderly, aged 70 and over. Changes in physiology have been well documented; for example, disturbances in hormonal modulation, abnormal regulation of carbohydrate and lipid metabolism, alterations in drug metabolism. There is a respectable, although spotty, literature on genetic

variability in older people that cannot be ignored in risk assessment analyses. Variability in responses to drugs, for example, are well documented as being due to genetic differences; these responses are frequently compounded by age differences as well.

The problem of risk assessment and setting of exposure standards is a partly scientific and a partly political one. We are proposing to hold a Symposium to discuss the scientific evidence for human variability. Our meeting, for the first time, will bring together knowledge of human heterogeneity as a coherent whole. We will then consider how the introduction of this new factor might affect risk assessment analyses. Accordingly, we will invite presentations from internationally recognized experts from the fields of human epidemiology, toxicology, genetics, carcinogenesis and teratology. Our discussions may demonstrate the scope and extent of variation in "normal" populations, and reduce scientific uncertainties in this area. But since the resolution and obligations of risk assessment are, in the last analysis, a political process, we also shall involve in our program experts from the regulatory agencies concerned in risk analysis, so that the scientific and political processes go hand-in-hand.

The Biology and Medical Departments at Brookhaven National Laboratory have sponsored scientific symposiums for many years and our staff have a great deal of expertise in assuring that the meeting will be successful and rewarding for all participants. Our support systems are in place and we can accommodate up to 250 participants in housing on site. We have secured a publisher for the proposed symposium proceedings.

We append a tentative program, with possible speakers, many of whom have already expressed their eagerness to participate.